

**REMARKS**

Applicants are amending their claims in order to further clarify the definition of various aspects of the present invention. Specifically, Applicants have amended claim 1 to recite that the method includes visualizing and identifying an individual chain molecule uprightly immobilized on the substrate. Similarly, claim 19, the only other independent claim being considered on the merits in the above-identified application, has been amended to recite that the method includes visualizing and identifying an individual chain molecular uprightly immobilized on the substrate, further defining that this individual chain molecule immobilized on the substrate is a nucleic acid. See. e.g., the paragraph bridging pages 25 and 26 of Applicants' specification. Moreover, Applicants have cancelled claim 20 without prejudice or disclaimer.

Initially, it is respectfully requested that the present amendments be entered. Noting previously considered claims in the application, including previously considered dependent claims such as claims 2 and 20, and also noting previous arguments made in connection with the above-identified application in the Amendment filed September 12, 2007, it is respectfully submitted that the present amendments do not raise any new issues, including any issue of new matter. Thus, note, for example, the paragraph bridging pages 25 and 26 of Applicants' specification, disclosing that in accordance with use of the molecular detection system described in the present application, "since molecules can be individually recognized", compared with the conventional detection method, detection is possible with a small amount of sample, a high sensitivity detection method can be provided, and, furthermore, the size of the chip, array, etc., can be reduced. In addition, by further defining the material visualized and identified, it is respectfully submitted that

the present claims materially limit issues remaining in connection with the above-identified application; and, as discussed infra, the present amendments at the least present the claims in better form for appeal. Noting the new grounds for rejection in the Office Action mailed November 26, 2007, and new arguments by the Examiner therein, it is respectfully submitted that the present amendments are clearly timely.

In view of the foregoing, it is respectfully submitted that Applicants have made the necessary showing under 37 CFR 1.116(b)(3); and that, accordingly, entry of the present amendments is clearly proper.

Applicants respectfully submit that all of the claims presented for consideration by the Examiner patentably distinguish over the teachings of the documents applied by the Examiner in rejecting claims in the Office Action mailed November 26, 2007, that is, the teachings of U.S. Patent Application Publication No. 2003/0013111 to Henderson, et al., and the article by Liu, et al., "Production of Nanostructures of DNA on Surfaces", in Nano Letters, Vol. 2, No. 8 (2002), pages 863-867, under the provisions of 35 USC 102 and 35 USC 103.

It is respectfully submitted that the teachings of these documents as applied by the Examiner would have neither disclosed nor would have suggested such a molecular detection method as in the present claims, wherein the material visualized and identified is an individual chain molecule uprightly immobilized on a plastic substrate, with such visualizing and identifying of this specified material being performed by probing with a scanning probe electron microscope in solution (see claims 1 and 19); in particular, wherein the chain molecule immobilized on the substrate, which is visualized and identified, is a nucleic acid (see claim 19).

Additionally, it is respectfully submitted that the teachings of the applied documents would have neither disclosed nor would have suggested such molecular

counting method as in the present claims, including detecting a molecule by the method of claims 1 and 19, and counting the number of detected chain molecules per unit area (see claims 6, 7, 23 and 24); or the molecular localization detection method, as in the present claims, wherein counting of the number of detected chain molecules per unit area gives molecular localization information (see claims 7 and 24).

Furthermore, it is respectfully submitted that the teachings of these applied documents would have neither disclosed nor would have suggested such a production process for a substrate with a chain molecule immobilized thereon, this process including the method according to claim 1 or 19 (see claims 17 and 25).

In addition, it is respectfully submitted that the teachings of the applied documents would have neither disclosed nor would have suggested such molecular detection method as in the present claims, having features as discussed previously in connection with claims 1 and 19, and, additionally, wherein the chain molecule is an uprightly disposed single strand molecule (note claim 2); and/or wherein the uprightly disposed single strand molecule is a molecule selected from the specific group of substances as in claim 3; and/or wherein the chain molecule immobilized on the substrate is a multiple strand molecule comprising an uprightly disposed single strand molecule (comprising the nucleic acid) and at least one chain molecule that binds to the single strand molecule (nucleic acid), as in claims 4 and 21; and/or wherein the multiple strand molecule is a complex as in claims 5 and 22.

The present invention relates to a molecular detection method, which can be used to visualize and identify localized chain molecules.

In immobilizing DNA on a substrate, there are known techniques in which DNA is directly synthesized on a substrate, and in which DNA, that has been

synthesized separately, is immobilized on a substrate. In each of these techniques, unless the DNA is uniformly and distributedly (nonlocalized) immobilized on an intended section on the substrate, qualitative and quantitative analytic performance cannot be exhibited. Conventionally, there is no technique for examining, at the molecular level, whether or not, e.g., single strand DNA is uniformly immobilized on a specific area on the substrate, and there has been a desire for development of such a testing technique.

As described in the paragraph bridging pages 2 and 3 of Applicants' specification, with regard to means for obtaining information on whether or not immobilized molecules are nonlocalized or localized on a substrate, there is observation using an electron microscope; however, since this observation is carried out under vacuum, in the case of biopolymers the structure thereof will be destroyed and observation is not possible, or they stick to the substrate, thus making it impossible to distinguish them from the substrate.

Thus, there is a desire for a molecular detection technique that enables, in a substrate such as a DNA chip or a DNA microarray in which a large number of chain molecules are immobilized, the individual molecules to be visualized and counted while maintaining activity of the chain molecules; and, moreover, wherein information about localization of the molecules can be obtained.

Against this background, Applicants provide a technique achieving the objects referred to previously. Specifically, Applicants provide a technique wherein an individual chain molecule is visualized and identified easily and accurately, with such individual chain molecule uprightly mobilized on a plastic substrate in solution, the visualizing and identifying being performed by probing with a scanning probe microscope.

Accordingly, by the present invention using a plastic substrate, a relatively inexpensive substrate is utilized; and, moreover, the chain molecules immobilized on the substrate can be clearly detected, and the molecules can be identified, with information about localization obtained.

Moreover, since the molecules can be individually recognized, as compared with conventional detection methods wherein an array is visualized, detection is possible with a small amount of sample, and a high sensitivity detection method is achieved. Note, for example, the paragraph bridging pages 25 and 26 of Applicants' specification.

Henderson, et al. discloses an apparatus and method for the construction and utilization of molecular deposition domains. This patent document focuses on measuring molecular events in arrays, which provide a large number of test sights in a relatively small area. Note paragraph [0007] on page 1 of this patent publication; note also the definition of "array" in paragraph [0060] on page 4 of this patent document. This patent document discloses a method for the construction of a molecular deposition domain including providing a surface, depositing a deposition material on a deposition device, and depositing the deposition material on the surface using the deposition device, forming a molecular deposition domain smaller than 1 micron in total area. See paragraph [0044] on page 3 of this patent document; note also paragraph [0045] bridging pages 3 and 4. Note also paragraphs [0071] and [0073] on page 5, disclosing various substrates which can be used in any disclosed process.

It is respectfully submitted that Henderson, et al. does not disclose, nor would have suggested, such method as in the present claims, including visualizing and

identifying an individual chain molecule uprightly immobilized on a plastic substrate, or advantages achieved by the present invention due thereto.

The contention by the Examiner in the sole full paragraph on page 3 of the Office Action mailed November 26, 2007, referencing Fig. 11 and paragraph [0107] of Henderson, et al., that this patent document teaches a multiple strand chain molecule that "is an uprightly disposed single strand molecule", is respectfully traversed. Contrary to this contention by the Examiner, it is respectfully submitted that Henderson, et al. does not teach, nor would have suggested, a deposition material uprightly deposited; in this regard, attention is respectfully directed to paragraphs [0091]-[0096] on page 7 of Henderson, et al.

Furthermore, it is respectfully submitted that Henderson, et al. does not disclose, nor would have suggested, visualizing and identifying an individual chain molecule uprightly immobilized, much less such visualizing and identifying "by probing with a scanning probe microscope in solution", as in the present claims, and advantages thereof as discussed previously.

It is respectfully submitted that Henderson, et al. teaches scanning the array after taking the array out of a medium. As described in paragraphs [0104] and [0106] of Henderson, et al., the exposure time of the array to the medium depends on what type of molecular interaction events the user may be studying, and after the molecule deposition array 66 (note Fig. 11 of Henderson, et al.) is exposed to the test medium, it may be scanned by the AFM. It is respectfully submitted that these sentences mean that the array is dipped in the medium for a while, and subsequently the array is taken out of the medium. It is respectfully submitted that such disclosure in Henderson, et al. would have taught away from the visualizing

and identifying the specified molecule by probing with a scanning probe microscope in solution, as in the present invention, and advantages thereof.

It is respectfully submitted that the additional teachings of Liu, et al. would not have rectified the deficiencies of Henderson, et al., such that the presently claimed invention as a whole would have been obvious to one of ordinary skill in the art.

Liu, et al. discloses development of three AFM (atomic force microscopy)-based lithography techniques for creating nanopatterns of self-assembled monolayers (SAMs) and biosensors; and discloses that using these methods, nanostructures of thiols as small as  $2 \times 4\text{nm}^2$  have been produced with various chain lengths and terminal groups such as  $-\text{OH}$ ,  $-\text{CO}_2\text{H}$ ,  $-\text{NH}_2$  and  $-\text{CHO}$ . Therein, this article discloses that in addition to SAM nanostructures, biomolecules such as proteins can be positioned on a surface via selective immobilization; and further discloses that to take full advantage of AFM lithography, application of nanografting in patterning single-stranded DNA (ssDNA) has been tested. Note especially the procedure for fabricating DNA nanopatterns, in Fig. 2 on page 864 of this article, and described in the last paragraph in the left-hand column on page 864. See also Figs. 3 and 4 thereof, respectively on pages 865 and 866 of this article.

Even assuming, arguendo, that the teachings of Liu, et al. were properly combinable with the teachings of Henderson, et al., such combined teachings would have neither disclosed nor would have suggested the present invention, including, inter alia, visualizing and identifying an individual chain molecule uprightly immobilized on a substrate, or other features of the present invention as discussed previously. In this regard, note that in Figs. 3 and 4 of Liu, et al., a square, rectangle or line of ssDNAs is shown. It is respectfully submitted that the square, rectangle or line of the ssDNAs is an aggregate of ssDNAs, and that the Liu, et al. teaches

visualizing and identifying the aggregate, teaching away from visualizing and identifying an individual chain molecule uprightly immobilized on a substrate, as in the present claims, and teaching away from processing wherein such visualizing and identifying of the individual chain molecule is performed by probing with a scanning probe microscope in solution.

In view of the foregoing comments and amendments, entry of the present amendments, and reconsideration and allowance of all claims then remaining in the above-identified application and being considered on the merits therein, are respectfully requested.

To the extent necessary, Applicants hereby petition for an extension of time under 37 CFR 1.136. Kindly charge any shortage of fees due in connection with the filing of this paper, including any extension of time fees, to the Deposit Account of Antonelli, Terry, Stout & Kraus, LLP, Account No. 01-2135 (case 1204.45527X00), and please credit any overpayments to such Deposit Account.

Respectfully submitted,

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